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Is a Vitamin Supplement Effective in Treatment of Recurrent Aphthous Ulcers?

Annalyse Grayson
Philadelphia College of Osteopathic Medicine, annalysegr@pcom.edu

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Abstract

Objective: The objective of this EBM review is to determine whether or not a daily vitamin supplement is effective treatment for recurrent aphthous ulcers.

Study Design: A review of 3 randomized control trials. All three trials are in English between 2009-2014.

Data Sources: 3 randomized double blind placebo-controlled parallel-arm single center trials were found using PubMed.

Outcomes Measured: Each of the RCTs measured the efficacy of treatment for RAU in patients with aphthous ulcer outbreaks for at least a year or at least one to three outbreaks a month. This was performed by subjects of the study reporting on efficacy of each a daily multivitamin, Omega-3 supplement or Vitamin B12 supplement following the recommended daily intake scale.

Results: All three RTCs were used in this review and it was determined that a daily vitamin supplement did not lead to any significant life-threatening conditions.

Conclusions: Based on the three trials, only the multivitamin supplement proved to be ineffective in the treatment of recurrent aphthous ulcers in adults. Both the Omega-3 and Vitamin B12 proved to be both cost-effective and improved the quality of life for patients with RAU.

Key Words: Recurrent Aphthous Ulcers, RAU, Canker Sores, Vitamin, Multivitamin, Omega-3, Vitamin B12

INTRODUCTION

Recurrent Aphthous Ulcers is a condition in which patients develop painful ulcerations in the mouth along the hard and soft palate, gum line, inner sides of the lips, sublingually and directly on the tongue. This may interfere with a person's ability to eat or maintain daily oral hygiene and speech secondary to pain.[1,2] Aphthous ulcers are categorized as minor, major and herpetiform lesions with minor being the most commonly seen.[2,3] RAU can be a debilitating disorder caused by painful ulcerations which heal and leave scars after several weeks and contribute to decreased quality of life and increased morbidity.[2] This paper reviews three randomized control trials detailing the efficacy of taking a daily vitamin supplement orally for the treatment of recurrent aphthous ulcers.

Recurrent Aphthous Ulcer disorder is the most common oral disorder in North America and affects 2.5 billion people world-wide.[1,2] Aphthous ulcers may indicate underlying disease and may act as an indicator for disorders like Celiac disease, however they may be a featured along with Behçet's and Inflammatory bowel disease.[4] Because of its relevance to this country and effects on quality of life it is relevant to the PA profession. The annual medical cost and healthcare visits regarding this disorder is unknown.

The exact cause of RAU is unknown however they are believed to be induced by physical, mental or emotional stress, autoimmune disorders and allergies and may even be related to genetics.[2] Certain foods including: Spicy, acidic or salty, citric fruits, chocolate and alcohols may trigger and prolong the duration of the ulcers.[5]

Current treatment regimens used to treat RAU include topical mouthwashes to systemic oral medications.[1] Determining associated features with RAU disorder may be beneficial in

selecting an appropriate treatment method. Topical agents used include: gel, creams, ointments or mouthwashes of Chlorhexidine, Hyaluronic acid and Amelanox.[3] If a patient does not respond to topical treatments they may require systemic treatment.[3] These treatments include: Colchicine, Levamisole and Corticosteroids.[3] Local anesthetics such as tetracaine and polidocanol or benzocaine and cetylpyridinium can be used for symptom relief but are not proven to treat the ulcer.[5] More significant measures taken to control ulcer eruption includes laser therapy and cryotherapy but should be performed by an oral specialist to avoid destroying healthy tissue surrounding the ulcer.[1,5]

There is no current solitary treatment or cure for RAU and without an exact cause identified it is difficult to determine the best route for success. However, there are successful treatment modalities, such as the ones listed above, for most patients which are consistent with the disease as it presents differently in each patient. This topic is nominated to address a more cost-effective and safe treatment option in order to decrease morbidity and increase the quality of life for patients suffering from RAU. The objective of this evidence based medicine review is to determine whether or not a daily vitamin supplement is effective treatment for recurrent aphthous ulcers.

METHODS

Three randomized double blind placebo-controlled parallel-arm single center trials were used in this study. The population included adult patients suffering from recurrent aphthous ulcers ranging from age thirteen and older. The intervention included a daily vitamin supplement: Multivitamins, Omega-3 and Vitamin B12. Each study was divided into two groups and compared to the placebo supplement for efficacy of treatment. All three of the studies also

described utilizing specific parameters for treatment efficacy including: decrease in pain, number of new outbreaks and duration of current ulcer outbreak.[2,3,4] In the beginning of Lalla's, Khouli's and Volkov's studies patients were measured at baseline and again at intervals determined by the study. In the Lalla study patients were given one generic multivitamin by mouth containing U.S. RDI of A, B1,B2, B3, B5, B6, B9, B12, C, D, and E[2]. The Khouli study had patients taking 1 g of Omega-3 orally TID and Volkov's study had patients taking 1000mcg of Vitamin B12 sublingually.[3,4]

Key words needed to research these articles included Recurrent Aphthous Ulcers, RAU, Multivitamin, Omega-3 and Vitamin B12. All three articles were researched using PubMed by the author. These articles were all published in English and published in peer-reviewed journals. These articles were chosen based on the relevance to the clinical question as well as being patient oriented outcomes. The inclusion criteria for this search included double-blind randomized control trials in which the outcome would directly affect the population involved. The exclusion criteria included patients who did not suffer from recurrent aphthous ulcers, Patients with a history of smoking, a diagnosis of any systemic condition causing oral ulcerations or liver, heart, renal, immune deficiency diseases, anemia, use of NSAIDs on a regular basis, or currently pregnant or lactating.[2,3,4] Statistics used in these studies include: Number needed to treat (NNT), P-Value, relative risk reduction (RRR) and absolute risk reduction (ARR). Table 1 displays the demographics as well as characteristics observed in the study.

Table 1. Demographics and Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Lalla (2012)	Double blind RCT	160	≥18 years old	≥18 years with a valid history of ≥ 3 episodes of aphthous ulcers within 12 months	Smoking, pregnancy, regular vitamin use, any over-the counter or Rx gents for RAS and a diagnosis of systemic condition causing oral ulcerations	60	1 Generic multivitamin by mouth containing U.S. reference daily intake of essential vitamins A,B1,B2,B3, B5,B6, B9, B12,C,D and E
Khouli (2014)	Double blind RCT	50	≥13 years old	≥13 years old, at least having minor RAU for ≥ 1 year with ≥ 1 outbreak per month	Patients with liver, heart kidney disease, pregnancy or lactation, systemic diseases giving rise to oral ulcers, anemia, or use of steroids, or NSAIDs on a regular basis	0	1 g Omega-3 3 times a day

Volkov[4] (2008)	Double blind RCT	58	≥18 years old	Patients suffering from RAS for ≥ 1 year with ≥ 2 outbreaks per month	Known systemic disease with associated oral ulcerations, B12 treatments in the past, pregnant, immune deficient, nursing mothers or psychotic patients	0	Sublingual dose of 1000 mcg of Vitamin B12 for 6 months

OUTCOMES MEASURED

The outcomes measured in this study were the duration of current ulcerations, and reduction in outbreaks of new ulcerations as well as pain level but this is not a primary outcome in any of the studies[2,3,4]. In Lalla's study the unpaired t test and the Chi Squared test was used.[2] In the Khouli study the Oral Health Impact Profile-14 questionnaire was used along with the Kolmogorov-Smirnov test of normality were used as well as an unpaired t test and paired t test[3]. In the Volkov study the Chi-Squared test, the Mann-Whitney and Friedman test were used to determine patient outcomes.[4] Patients were asked to subjectively report the number of outbreaks, duration in which the ulcers lasted and their pain levels in a diary in each study.[2,3,4]

RESULTS

This review investigated three RCTs including patients who suffered from Recurrent Aphthous Ulcers without an underlying systemic disease and compared the use of a daily multivitamin, Omega-3 or Vitamin B12 supplement for treatment of RAU. All three studies presented as dichotomous data and therefore assessment of efficacy of all three vitamin supplements was attainable[2,3,4].

In the Lalla Study those who smoked, used over-the-counter medications for RAU on a regular basis, were diagnosed with systemic diseases which caused oral ulcerations, or were currently pregnant or lactating were excluded from the study.[2] The control group had 58 participants receiving one generic multivitamin meeting RDI quality while the experimental group had 56 participants receiving the placebo treatment. The study showed that compared to baseline the multivitamin had no noticeable benefit over the placebo group. The number of new ulcers in the treatment arm was 4.19±4.74 with a p-value of 0.69 and in the control group was 4.60±4.58 with a p-value of 0.40 showing no significance in the use of a multivitamin for the treatment of aphthous ulcers. The number needed to treat in this study was calculated to be -0.26.[2] This means that for every 26 people taking a multivitamin supplement, 1 will not have a new occurrence of aphthous ulcers, compared to control.

Table 2. Duration of RAS for Lalla Study.[2]

Study Groups	**Duration in Days Mean+SD**	**p-value**
Multivitamin	8.66±4.60	0.60
Placebo	8.99±5.22	0.60

Table 3. Incidence of New Episodes. [2]

Group	**Number of New Episodes (Total)**	**Number of New Episodes Mean±SD**	**p-value**
Multivitamin	335	4.19±4.74	0.69
Placebo	329	4.60±4.58	0.40

In the Khouli study patients younger than thirteen years of age, patients with livers, heart, or kidney disease, systemic diseases with associated oral ulcers, anemia, the use of steroids on a

regular basis or pregnant and lactating females. These patients were assessed on the number of new ulcers, average duration and their overall quality of life recorded on the Oral Health Impact Scale.[3] The data collected showed a noticeable difference in the number of new ulcers from baseline compared to the placebo. With the Omega-3 supplement 6.40±4.83 new ulcers went to 0.76±1.05 and in the control group 6.72±4.60 changed to 6.28±4.99.[3] The p-value was < 0.05 showing a significance in the use of Omega-3 supplement for the treatment of aphthous ulcers. The numbers needed to treat was

Table 4. Mean duration of ulcers in Khouli Study.[3]

Timeline	**Omega-3 Group**	**Placebo**
Baseline	9.12+7.16	10.40+7.57
6 Months	1.76+1.89	8.60+4.26

Table 5. Mean number of monthly ulcers in Khouli Study.[3]

Timeline	**Omega-3 Group**	**Placebo**
Baseline	6.40±4.83	6.72±4.60
6 Months	0.76±1.05	6.28±4.99

In the Volkov study patients with known systemic diseases associated with oral ulcerations, vitamin B12treatments in the past, immunocompromised, pregnant, lactating or psychotic patients were excluded from this study.[4] The Volkov study showed a significant decrease in the number of new outbreaks as well as the duration in which the ulcers remained. The number of new ulcers in the treatment arm showed 3.88±7.98 and in the control group 13.39±23.56 exhibiting a significant difference with the use of Vitamin B12 supplement in the treatment of aphthous ulcers. The number needed to treat was calculated to be 0.02. This means

for every 2 people taking the vitamin B12 supplements, 1 person will not have a recurrence of ulcers after treatment.

Table 6. Duration of Aphthous Ulcers in Volkov Study.[4]

Groups	**Duration at 6 months Mean±SD**	**p-value**
Intervention	1.98±3.77	0.05
Control	4.84±5.71	0.05

Table 7. Number of New Ulcers in Volkov Study.[4]

Group	**Number of New Ulcers Mean ± SD**	**p-value**
Intervention	3.88±7.98	P <0.05
Control	13.39±23.56	P<0.05

Table 8. Treatment Effects

STUDY	**P-Value**	**CER**	**EER**	**RRR**	**ARR**	**NNT**
Lalla	P < 0.69	51.9%	48.1%	-0.07%.	-3.8%	-26
Khouli	P < 0.05	-	-	-	-	-
Volkov	P < 0.0001	32%	74%	1.31%	-42%	-2

DISSCUSSION

Recurrent Aphthous Ulcers is a disorder in which ulcerations inhabit the oral cavity causing pain, decreased ability to eat and sometimes speak and ultimately affects the quality of life.[1] There is no known cause of aphthous ulcers but there is an understanding of triggers for the outbreak of ulcers including: stress, allergies, genetics and diet. Limitations of the study

included compliance of subjects to takes medication as directed and report honestly as requested in the journals given.

CONCLUSION

This review and the chosen studies showed different outcomes for the treatment of Aphthous ulcers. Two of the studies promised benefits from the use of Vitamin B12 and Omega-3 supplements for the treatment and prevention of recurring aphthous ulcers. A Multivitamin containing RDI of vitamins A, B1, B2, B3, B5, B6, B9, B12, C, D, and E did not show promising results for treatment of RAS. All studies resulted in no harmful effects for the subjects involved but only two studies showed evidence of improved quality of life. Further studies with indications to utilize vitamin supplements for the treatment of RAS would benefit from a larger sample size. In the future, developing a longitudinal study with a more robust sample size would be beneficial. A sample size taken from various countries as opposed to just one institution would also improve study conditions. Indicating when the ulcers are present to determine if subjects have certain triggers may be beneficial to narrowing inclusion and exclusion criteria. Utilizing physicians of various fields such as ear nose and throat, oral surgeons and dentists to interpret patterns in the studies would be beneficial for study outcomes as well as patient follow ups.

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